



REVIEW ARTICLE OPEN

Review of a new bone tumor therapy strategy based on bifunctional biomaterials

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Bone tumors, especially those in osteosarcoma, usually occur in adolescents. The standard clinical treatment includes chemotherapy, surgical therapy, and radiation therapy. Unfortunately, surgical resection often fails to completely remove the tumor, which is the main cause of postoperative recurrence and metastasis, resulting in a high mortality rate. Moreover, bone tumors often invade large areas of bone, which cannot repair itself, and causes a serious effect on the quality of life of patients. Thus, bone tumor therapy and bone regeneration are challenging in the clinic. Herein, this review presents the recent developments in bifunctional biomaterials to achieve a new strategy for bone tumor therapy. The selected bifunctional materials include 3D-printed scaffolds, nano/microparticle-containing scaffolds, hydrogels, and bone-targeting nanomaterials. Numerous related studies on bifunctional biomaterials combining tumor photothermal therapy with enhanced bone regeneration were reviewed. Finally, a perspective on the future development of biomaterials for tumor therapy and bone tissue engineering is discussed. This review will provide a useful reference for bone tumor-related disease and the field of complex diseases to combine tumor therapy and tissue engineering.

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INTRODUCTION

Bone tumors involve the invasion of tumors into bone tissue and are classified as either primary tumors or metastatic tumors. Osteosarcoma is a well-known primary malignant bone tumor that often occurs in children and adolescents. It has been reported that this disease has become the second leading cause of tumor-related death in young teenagers.¹ The majority of patients die from lung metastases. Its annual incidence worldwide is ~1–3 cases per million.² The clinical signs of osteosarcoma are not obvious without spontaneous fracture or severe pain early on. Therefore, this disease is not easily diagnosed, but the tumors grow quickly. As a result, osteosarcoma causes a large bone defect and limitations in motion and can metastasize to the lungs.³ The etiology of osteosarcoma is still not clear.⁴ To date, the most common clinical treatment methods for bone tumors include chemotherapy, wide surgical resection, and radiotherapy.⁵ However, osteosarcoma is not sensitive to radiotherapy and is prone to chemotherapy resistance. Surgical resection often fails to completely remove the tumor, which is the main cause of postoperative recurrence and metastasis. Moreover, osteosarcoma invades large areas of bone, which cannot repair itself, and has serious effects on the quality of life of patients.⁶ The 5-year survival rate of patients with osteosarcoma is ~60%.⁷ Unfortunately, advances in osteosarcoma treatment have reached a plateau over the past 40 years.⁸

Metastatic bone tumors start somewhere else in the body and then spread to bone tissue at a later stage. Bone tissue is one of the most common metastatic sites, and certain cancers, such as breast, prostate, colon, and lung cancer, are closely related to bone metastasis.^{9–13} Bone metastasis results from tumor cells

migrating and adhering to the bone, thus interfering with the balance of bone formation and bone resorption. Osteosarcoma and bone metastasis share some similarities,¹⁴ but metastatic bone tumors exist in the later stage of the tumor. The primary tumor is usually diagnosed before it metastasizes to the bone after treatment. In tumor-induced bone defects, metastatic bone tumors and osteosarcoma share similar tumor niches and microenvironments. Innovative and efficient therapeutic strategies are urgently needed to solve the problems in the treatment of bone tumors.¹⁵

Along with the development of bionanotechnology, new innovative treatment options have been designed for bone tumor therapy. Bone tumor therapy combines the complex issues of tumor therapy and bone regeneration, which demand functional biomaterials for treatment. It is challenging to design novel strategies with the dual capabilities of both preventing tumor recurrence and supporting bone formation, demanding an interdisciplinary research background.^{16,17} Many researchers worldwide have focused their efforts on solving these bone tumor treatment problems. Although they are only in the early stages of development, new treatment methods have brought great hope to finding a cure for bone tumors.

Traditional postoperative bone tumor treatment is chemotherapy. However, these chemical drugs can lead to systemic side effects such as liver dysfunction, heart toxicity, and bone marrow suppression. The development of new supplementary or alternative tumor treatment methods based on biomaterials can avoid these side effects by selective delivery.^{18–26} Specifically, photothermal therapy is an emerging treatment method that converts near-infrared (NIR) light into localized thermal

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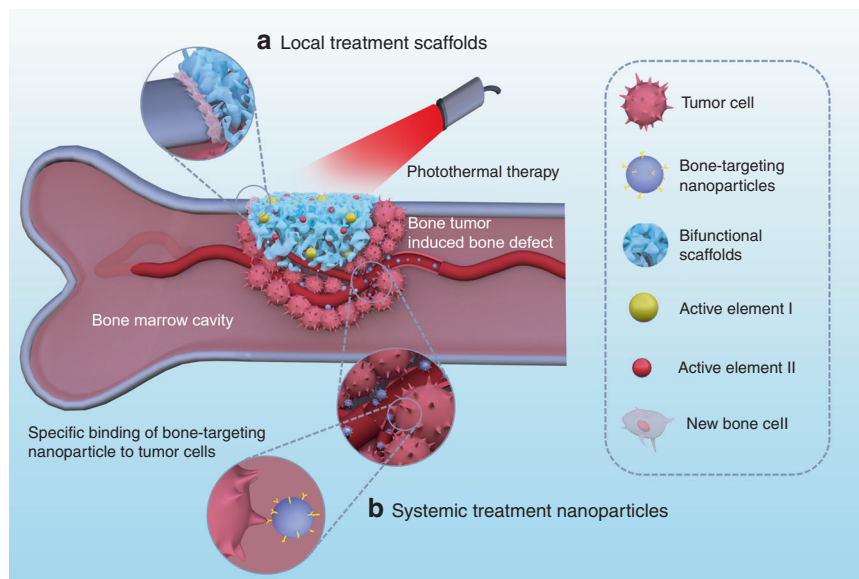


Fig. 1 Bifunctional biomaterials include (a) local treatment scaffolds (such as 3D-printed scaffolds, nano/microparticle-containing scaffolds, and hydrogels) and (b) systemic treatment nanoparticles (such as bone-targeting nanoparticles) for tumor photothermal therapy and bone regeneration

energy to destroy tumor tissue.^{27–35} Photothermal therapy is based on nanomaterials with strong NIR absorption, such as gold nanoparticles,^{36–41} carbon nanomaterials,^{42,43} magnetic nanoparticles,^{44–48} and copper nanomaterials.^{49,50} Photothermal therapy is suitable for localized tumor therapy due to the concentrated irradiation region of the laser and its ability to limit the deep penetration of heat without damaging other organs or tissues.^{51–55} With its rapid development, photothermal therapy is a potential supplement to preclinical and clinical tumor therapy. For example, photothermal therapy based on gold nanoshells has shown a great therapeutic effect in clinical trials for prostate tumor therapy.^{56,57} Photothermal therapy is a suitable candidate method for bone tumor treatment, and related studies have focused on it.

Due to the offensive spreading of tumors into bone, bone metabolism becomes unbalanced. Healthy bone tissue is resorbed and invaded by the tumor, leading to bone defects. After tumor therapy, these bone defects become the next issue of concern. Bone tissue engineering is a fascinating field that gives hope to bone regeneration. The biomaterial scaffolds developed for bone tissue regeneration include nanofibers, 3D-printed scaffolds, hydrogels, microspheres, and nanoparticles.^{58–64} Bioactivity, biocompatibility, and biodegradability are critical concerns in scaffold design, playing an important role in bone regeneration.^{65–68} In particular, the key parameters of porosity, stiffness, and viscoelasticity can regulate cell adhesion, cell proliferation, and osteogenesis differentiation.^{69–76} Scaffolds provide cells with sustainable regenerative factors, provide physical and biological support, and mobilize stem cells to regenerate the defect cavity.^{77–82} Bifunctional scaffolds have been designed in recent years, thanks to the tireless work of researchers, for tumor photothermal therapy and bone repair. These scaffolds are capable of simultaneously providing tumor therapy and enhanced bone regeneration, a useful “two birds, one stone” strategy. Figure 1 shows a bone tumor that was killed by bifunctional biomaterials through either local or systemic administration. The locally administered bifunctional scaffolds (such as 3D-printed scaffolds, nano/microparticle-containing scaffolds, and hydrogels) were inserted into the bone defect area for tumor photothermal therapy and, subsequently, improved bone repair. The systemically

administered nanoparticles penetrated blood vessels to target the bone tissues for tumor treatment and to inhibit bone reabsorption. Some representative examples of bifunctional biomaterials were summarized and listed in Table 1.

This review provides details of the recent developments in the use of bifunctional biomaterials to achieve bone tumor therapy. The new strategies in bifunctional biomaterial preparation and treatment methods are presented in the main text. Bone tumor therapy by bifunctional biomaterials is an important development direction for bone tissue engineering.⁸³ Moreover, bifunctional biomaterials will play a vital role in the therapy of complex diseases, which combine tumor therapy and tissue engineering (including bone tissue engineering, skin tissue engineering, adipose tissue engineering, etc.).

A NEW STRATEGY FOR TUMOR THERAPY AND BONE REGENERATION

The rapid proliferation and invasion of osteosarcoma cancer cells is still the main reason why the survival rate of osteosarcoma patients has not improved in decades. Therefore, there has become an urgent need to explore new ways to treat osteosarcoma. Biomaterials for bone tumor therapy need to possess two functions: killing tumor cells and helping bone regeneration. For administration, we divided the bifunctional biomaterials into local treatment and systemic treatment options. The local bifunctional biomaterials for bone tumor therapy concentrate mainly on 3D-printed scaffolds, nano/microparticle-containing scaffolds and hydrogels. The representative systemic treatment biomaterial is bone-targeting nanoparticles for bone tumor therapy. Therefore, in this section, we present and discuss recent research on these strategies for tumor therapy and bone regeneration.

Local treatment

3D-printed scaffolds. The new, innovative technology of 3D printing was first proposed by Prof. Ely Sachs.⁸⁴ Through its rapid development, 3D printing is now widely applied in the field of tissue engineering.^{85–88} The bioactive ions in 3D-printed scaffolds, such as Ca^{2+} , P^{5+} , Si^{4+} , Mg^{2+} , Fe^{3+} , and Mn^{4+} , can improve osteogenic activity.^{89–95} In only a few years, a series of

Table 1. Examples of bifunctional biomaterials mainly include 3D-printed scaffolds, nano/microparticle-containing scaffolds, hydrogels, and bone-targeting nanomaterials in tumor therapy and bone regeneration

Platform	Biomaterial	Tumor therapy	Bone regeneration	Ref.
3D-printed scaffolds	3D-printed Fe-CaSiO ₃ scaffold	Synergistic photothermal and ROS therapy enhanced Saos-2 bone tumor therapy in the backs of nude mice	The active elements Fe, Ca, Si in the scaffold enhanced large bone defect repair in rabbits	99
	Silicone resin-derived larnite/C 3D-printed scaffold	Photothermal effect inhibited MNNG/HOS human osteosarcoma tumor growth in nude mice	Promotion of bone formation in critical-sized rat calvarial defect by stimulating an osteogenesis-related gene	101
	Coloaded CaO ₂ and Fe ₃ O ₄ nanoparticle 3D-printed biomaterial	Reactive oxygen species therapy and magnetic hyperthermia produced a synergistic effect in MNNG/HOS osteosarcoma tumor-bearing BALB/c nude mice	Ca ²⁺ ions released from CaO ₂ nanoparticles improved the bone regeneration in SD rats cervical defects	102
Nano/microparticle-containing scaffolds	SrFe ₁₂ O ₁₉ nanoparticle modified-mesoporous bioglass/chitosan porous scaffold	Photothermal therapy in MG-63 bone tumors	Bone regeneration in a critical calvarial defect model	110
	Chitosan matrix incorporated Fe ₃ O ₄ nanoparticles and GdPO ₄ nanorods	Photothermal effects to avoid postoperative cancer recurrence in MDA-MB-231 breast tumors in nude mice	GdPO ₄ nanorods in the scaffold as a bioactive component enhanced stabilizing angiogenesis in calvarial defects	112
	Fe ₃ O ₄ loaded in a polymethylmethacrylate (PMMA) bone cement scaffold	An alternating magnetic field induced magnetic nanoparticles for thermal ablation of an in situ bone tumor model	The PMMA-Fe ₃ O ₄ scaffold with good mechanical support enhanced bone repair in a tibial plateau bone tumor rabbit model	113
Hydrogels	Hydrogenated black TiO ₂ (H-TiO ₂) coating with biomimetic hierarchical micro/nanostructures deposited on a titanium implant	Photothermal therapy induced necrosis of Sao-2 bone tumor cells in vitro and in vivo	The hierarchical micro-/nanotopography on an implant improved the adhesion, proliferation and osteogenic differentiation of BMSCs in vitro	115
	Polydopamine and cisplatin decorating an n-HA surface loaded in chitosan/alginate hydrogels	Photothermal therapy and chemotherapy for 4T1 breast tumor-bearing mice	The bifunctional hydrogel induced bone repair in the joint bones of rabbits	136
	Nanohydroxyapatite hybrid reduced graphene oxide (nHA-rGO) hydrogel	The nHA-rGO hydrogel induced photothermal therapy and killed almost all MG-63 osteosarcoma cells in vitro and in vivo	The nHA-rGO hydrogel promoted bone regeneration with the stimulation of osteoblast mineralization and collagen deposition in a rat cranial defect model	105
Bone-targeting nanomaterials	Gold nanorods enclosed inside mesoporous silica nanoparticles conjugated with zoledronic acid (Au@MSNs-ZOL)	Photothermal therapy enhanced by targeting to treat breast cancer bone metastasis, which was established by direct injection of MDA-MB-231 cells into the left hindlimbs of nude mice	Bone-targeting assisted inhibited the formation of osteoclast-like cells and promoted osteoblast differentiation	167
	Phytic acid (PA)-capped platinum (Pt) nanoparticles	Photothermal therapy of Pt nanoparticles and anticancer capabilities of PA were enhanced by tumor targeting for PC-9-Luc bone tumors in nude mice	PA/Pt nanoparticle-associated combination therapy inhibited osteolysis in the tibias of tumor-bearing nude mice	169

3D-printed bifunctional ceramic scaffolds for tumor therapy and bone repair have been developed. Some outstanding work in this field has been done by Chengtie Wu's group.^{96,97} For example, a 3D-printed scaffold modified with a Ca-P/polydopamine nanolayer was formulated by their group.⁹⁸ The polydopamine nanoparticles used on the surface can cause hyperthermia to kill MDA-MB-231 tumors in nude mice. Additionally, this scaffold can release Ca and P in a sustainable manner to induce femoral defect regeneration. Moreover, a high-strength 3D bioscaffold with Fe-CaSiO₃ was designed and prepared for tumor therapy and bone repair (Fig. 2).⁹⁹ The 3D-printed Fe-CaSiO₃ scaffold possessed the high compressive strength of 126 MPa, contributing to the high inherent

mechanical properties of Fe. The high mechanical strength of this scaffold meets the load-bearing application requirements of human bone. Fe nanoparticles not only can provide photothermal therapy due to localized surface plasmon resonance but also can promote H₂O₂ decomposition to generate reactive oxygen species (ROS). Thus, synergistic photothermal and ROS therapies can enhance Saos-2 bone tumor inhibition. Furthermore, large bone defects in the legs of rabbits were repaired by an Fe-CaSiO₃ scaffold. Recently, β-tricalcium phosphate 3D-printed scaffolds (TCP-PDLLA-LB) modified with LaB₆ micro-nanoparticles/poly(D,L-lactide) were fabricated for tumor photothermal therapy and bone repair.¹⁰⁰ Lanthanum and boron, as a "bone-seeking" element and a trace element, respectively, are

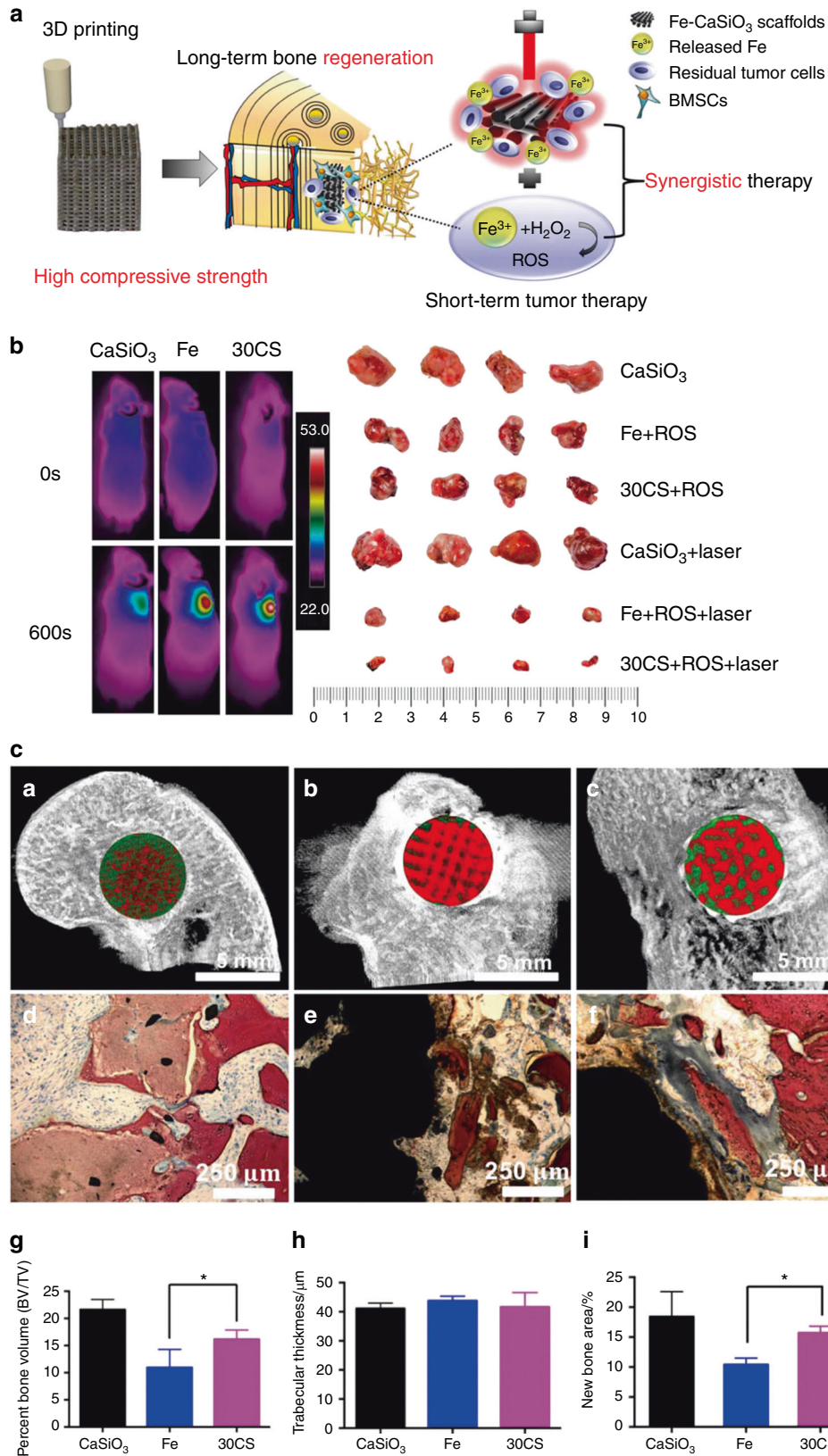


Fig. 2 3D printing of Fe-CaSiO₃ composite scaffolds for tumor therapy and bone regeneration. **a** The fabrication of Fe-CaSiO₃ composite scaffolds for short-term tumor therapy and long-term bone regeneration. **b** Infrared (IR) radiation thermal images of tumor-bearing mice after irradiation with an 808 nm laser for 600 s. The photographs of the tumors from the six groups are from day 15. **c** Micro-CT images (**a–c**) and histological analysis (**d–f**) of the bone defects in the CaSiO₃, Fe, and Fe-CaSiO₃ (30CS) groups postsurgery in a rabbit critical-sized femoral defect model. The statistical analysis of the defects (**g, h**) and histomorphometric measurements of *in vivo* osteogenesis (**i**) in the CaSiO₃, Fe, and 30CS groups 8 weeks post surgery. Reprinted with permission from ref. ⁹⁹ © 2018, Nature Publishing Group

bioactive, and their complex LaB_6 possesses NIR photothermal conversion properties. Therefore, the bone tumors were significantly suppressed by photothermal therapy. Regardless of NIR laser irradiation, TCP-PDLLA-LB 3D-printed scaffolds effectively assisted in new bone formation.

In a recent example, a larnite/C 3D-printed scaffold showed an excellent photothermal effect, killing MNNG/HOS human osteosarcoma cells and inhibiting tumor growth in nude mice.¹⁰¹ Additionally, the multifunctional 3D-printed scaffold enhanced bone formation in a rat calvarial defect model. In another related study, an "all-in-one" 3D-printed biomaterial coloaded with calcium peroxide (CaO_2) and iron oxide (Fe_3O_4) nanoparticles was used to solve the abovementioned dilemma in osteosarcoma therapy.¹⁰² The CaO_2 produced sufficient H_2O_2 in the acidic tumor environment, and the Fe_3O_4 nanoparticles generated toxic ROS via a Fenton-like catalytic reaction. Along with magnetic hyperthermia, these two agents can produce a synergistic effect in MNNG/HOS osteosarcoma tumor-bearing BALB/c in nude mice. Importantly, the CaO_2 nanoparticles released calcium ions to improve bone regeneration in SD rats cervical defects.

In the orthopedic field, there have been clinical trials in recent years in which 3D-printed personalized titanium plates were applied to bone defects.¹⁰³ Inspired by their utility and encouraging clinical outcomes, Mao et al. designed and fabricated titanium plates *via* computer-aided design and computer-aided manufacturing techniques customized and fixed to the patients' bone defects after the tumor was removed.¹⁰⁴ Twelve patients with osteosarcoma had their bone tumor tissues surgically removed and were then treated with microwave-induced hyperthermia to kill the residual tumor cells. Subsequently, allograft bone and poly(methyl methacrylate) (PMMA) cement were applied to fill the bone defect. Finally, the 3D-printed personalized plate was fixed to strengthen the bone segment. Hyperthermia and 3D plate therapy improved the clinical outcomes in terms of the mean maximum flexion of the affected knees and the Musculoskeletal Tumor Society score.

Nano/microparticle-containing scaffolds. Nano/microparticle-containing scaffolds usually refer to inorganic-organic hybrid scaffolds. Particle-containing bifunctional hybrid scaffolds are the desired design for bone tumor therapy.^{105–107} Microspheres composed of calcium phosphate-phosphorylated adenosine were prepared with high doxorubicin (DOX) loading for bone tumor therapy.¹⁰⁸ The pH-sensitive properties of microspheres presented a positive therapeutic effect on subcutaneous 143B osteosarcoma tumors in rats. Additionally, the hybrid microspheres can release active molecules to promote osteogenic differentiation *in vitro*. The study showed the potential application of calcium phosphate-phosphorylated adenosine microspheres for tumor inhibition and bone repair.

Additionally, a multifunctional magnetic mesoporous calcium silicate/chitosan (MCSC) porous scaffold that consisted of M-type ferrite particles ($\text{SrFe}_{12}\text{O}_{19}$), mesoporous calcium silicate (CaSiO_3), and chitosan was prepared.¹⁰⁹ The $\text{SrFe}_{12}\text{O}_{19}$ particles improved the photothermal efficacy with DOX-induced chemotherapy to reduce bone tumors. The MCSC hybrid scaffold upregulated indicators for osteogenesis. The data indicated that the MCSC hybrid scaffold promoted human bone marrow stromal cells to differentiate into osteogenic cells. In another study by the same author,¹¹⁰ fabricated $\text{SrFe}_{12}\text{O}_{19}$ nanoparticles containing bioglass/chitosan scaffolds also showed good bone repair of calvarial defects in rats.

Organic and inorganic materials are typically combined for complex disease in bone tumor treatment. Inorganic biomaterials, including nHA, TCP, bioglass, and bioceramics supply nutrients for tumor-defective bone repair. In a recent study,¹¹¹

the surface of beta-tricalcium phosphate bioceramic (β -TCP) materials was coated with carbon aerogel, which was developed for MNNG/HOS osteosarcoma tumor therapy. The carbon aerogel coating particularly enhanced the roughness and surface area of β -TCP, resulting in good bone regeneration in a calvarial defect model.

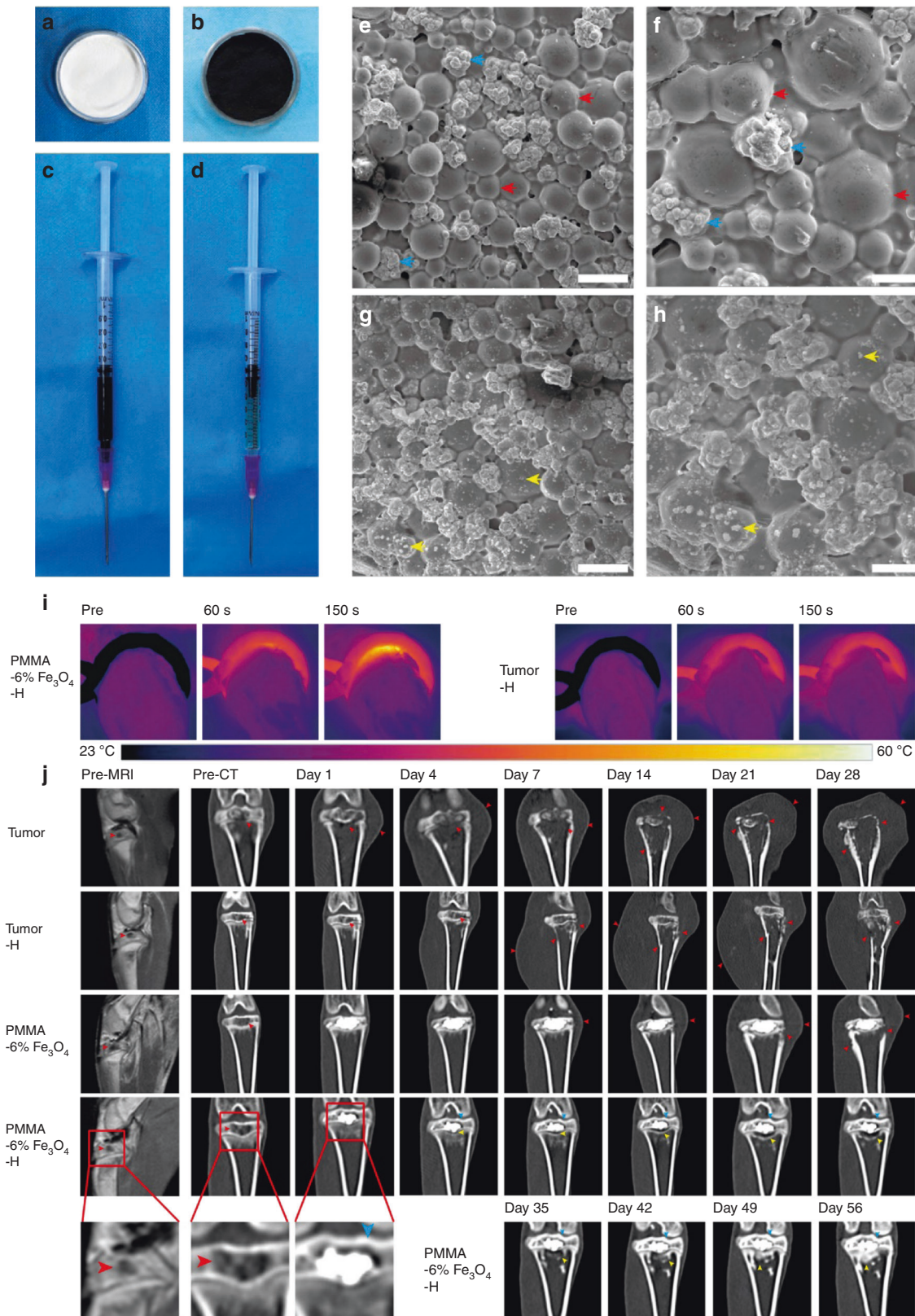
Breast cancer-induced bone metastasis is shown to cause cancer recurrence and local bone defects. A multifunctional magnetic chitosan matrix incorporating Fe_3O_4 nanoparticles and GdPO_4 nanorods was utilized for breast tumor therapy and bone defect regeneration.¹¹² The Fe_3O_4 nanoparticles in the scaffold supplied a high temperature through photothermal effects every other day for 14 days to avoid postoperative cancer recurrence in MDA-MB-231 tumor-bearing mice. Additionally, the GdPO_4 nanorods became orderly arranged in the scaffold and acted as a new bioactive component to induce M2 polarization of macrophages for enhanced stabilizing angiogenesis in the calvarial defect.

Another scaffold was developed from Fe_3O_4 magnetic nanoparticles containing PMMA bone cement with mechanical support, magnetic photothermal ablation, and bone repair features (Fig. 3).¹¹³ The liquid phase of these PMMA- Fe_3O_4 scaffolds can be accurately injected into the bone defect area. Once PMMA- Fe_3O_4 solidifies, an alternating magnetic field was used for the thermal ablation of the bone tumor. The fast phase transition of the PMMA- Fe_3O_4 scaffold prevented the leakage of Fe_3O_4 nanoparticles, which were nonbiodegradable during the long recovery period. Fortunately, good mechanical support is useful for physical function reconstruction. To simulate the clinical characteristics of the bone tumor, the therapeutic efficacy of the PMMA- Fe_3O_4 scaffold was evaluated in the tibia a tumor-bearing rabbit. The excellent heating performance provided a good VX2 tibial plateau tumor ablation outcome. The PMMA- Fe_3O_4 scaffold was shown to be a promising and minimally invasive agent with great clinical translation potential for the treatment of bone tumors.

Another very smart strategy is to simultaneously integrate photothermal therapy and bioactivity for bone regeneration into a single material. Bismuth (Bi)-doped bioglass provides photo-induced hyperthermia and enhanced remineralized bone tissue.¹¹⁴ The high photothermal conversion of Bi was first reported in this study. The photothermal effects were controlled by managing the radiative and nonradiative processes. Under NIR light, Bi hybrid bioglass can efficiently kill bone tumors. Moreover, Bi promotes the proliferation, differentiation, and mineralization of osteogenic cells.

Titanium is widely used in the clinical application of dental implants and is also a good choice for bone tumor therapy applications. Zheng et al.¹¹⁵ prepared a hydrogenated black TiO_2 (abbreviated as H- TiO_2) coating with a hierarchical porous topography on a titanium implant. The H- TiO_2 coating surface has photothermal abilities and can induce necrosis of Saos-2 bone tumor cells. Considering that the micro/nanostructures on the implant improved the osteogenic differentiation of BMSCs, it is promising to hypothesize that BMSCs can migrate to the implant surface for bone defect regeneration. Further *in vivo* demonstrations of the defect repair results are needed.

Hydrogels. Hydrogels are very large meshes that can contain water and have similar properties to the extracellular matrix. Hydrogels possess a highly porous structure, good biocompatibility, biodegradability, and a capability to load growth factors, leading to good bone defect repair.^{116–119} Thus, hydrogels are good candidates for bone repair. Several studies have shown potential for the use of hydrogels in bone tissue regeneration. For bone tumor therapy, the hydrogel needs to also be capable of treating tumors. It is highly advised to administer drugs or



ingredients into the resected tumor area.^{120,121} Hydrogels can provide sustainable drug release for tumor illumination.^{122–125} Some hydrogels integrate interior antitumor activity with localized delivery in one system.¹²⁶ Localized cancer treatment by hydrogels can replace the need for systemic chemotherapy administered intravenously or orally.^{127–130} With the development of multifunctional hydrogels, their applications are not limited to tissue repair but also extend to tumor cure and bone repair.

The ideal hydrogel system requires favorable parameters with good biocompatibility, a porous structure, adhesion to the cavity, good mechanical properties, and injectability.¹³¹ Among them, an injectable hydrogel can fill or match irregular defects with a mild gelation process in a minimally invasive manner.^{132–135} Recently, an injectable hydrogel was formed via a Schiff base reaction between the amino group of chitosan and the aldehyde groups of oxidized sodium alginate.¹³⁶ As shown in Fig. 4, a hydrogel was mixed with nanohydroxyapatite (n-HA) to induce bone repair in the joint bone of a rabbit. Moreover, n-HA was decorated with polydopamine and cisplatin, which can supply photothermal therapy and chemotherapy to treat 4T1 breast tumor-bearing mice.

In another study, an in situ UV-crosslinked gelatin methacryloyl hydrogel-encapsulated liposome was formed for the local release of gemcitabine.¹³⁷ Drug release lasts for 4 days in vitro, resulting in excellent inhibition of osteosarcoma in BALB/c mice bearing MG63 tumors. Thermosensitive hydrogels are also popular for localized drug release. For example, thermosensitive poly(L-lactide-co-glycolide)-poly(ethylene glycol)-poly(L-lactide-co-glycolide) (abbreviated as PLGA-PEG-PLGA) hydrogels were used to load DOX, methotrexate and cisplatin for localized drug delivery.¹³⁸ Synergistic cytotoxic effects were found in the multiple drug-loaded hydrogels against osteosarcoma in vitro and in vivo. Furthermore, localized treatment caused no obvious harm to normal tissues.

A nanohydroxyapatite hybrid reduced graphene oxide (nHA-rGO) hydrogel was developed for tumor-related bone defects.¹⁰⁵ The nHA-rGO hydrogel killed almost all MG-63 osteosarcoma

cells via photothermal therapy. Additionally, this hydrogel promoted bone regeneration by stimulating osteoblast mineralization and collagen deposition in a rat cranial defect model.

Systemic treatment

In recent years, there has been strong growth in nanotechnology in the fields of biology, medicine, and pharmaceuticals. Nanosized drug-based delivery platforms have been extensively studied and used for the treatment of osteosarcoma. Various nanoparticles have emerged as effective drug delivery systems in osteosarcoma treatment. Osteosarcoma tumor-invaded bone destruction contributes to an imbalance between bone reabsorption by osteoclasts and bone reconstruction by osteoblasts. Bone reabsorption promotes bone destruction and tumor metastasis processes.^{139,140} Moreover, a vicious cycle exists in osteolytic metastasis with bidirectional interactions between osteoclasts and tumor cells.⁹ Due to the low blood flow in the bone (0.05–0.20 mL·min⁻¹ per gram)¹⁴¹ and blood–bone marrow barrier, targeted delivery of anticancer agents is highly recommended for bone tumor therapy. Moreover, a targeted delivery strategy shows great potential to solve systemic toxic effects and multidrug resistance, which are longstanding problems with the standard cancer chemotherapy treatment.^{142,143}

Bone-modifying agents with a high affinity for bone are used for active bone targeting, including alendronate,^{144–146} zoledronic acid,^{147–149} aspartic acid,¹⁵⁰ denosumab,¹⁵¹ and aptamers.^{152,153} Nanomaterials and their drug delivery systems have unique advantages for the treatment of bone tumors.^{154–158} Because bone is composed of organic matrices and inorganic minerals that are assembled at the nanoscale, and nanomaterials can assimilate into the bone microenvironment to heal diseased bone.^{159,160} Furthermore, targeted delivery systems based on nanotechnology can improve the treatment efficiency of bone tumors.^{161,162}

Bisphosphonate molecules can specifically bind to the bone hydroxyapatite matrix via the chelation of calcium ions, which negatively influence osteoclast activity.^{163,164} In the 1960s,

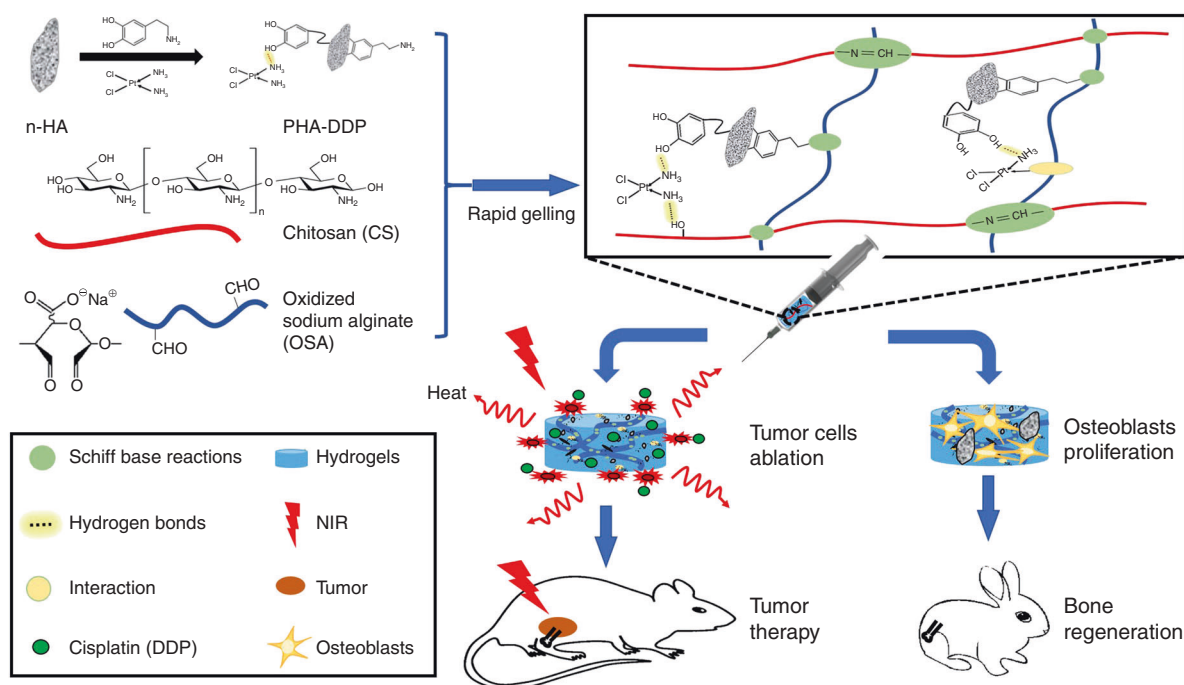


Fig. 4 The formation of a bifunctional OSA-CS-PHA-DDP hydrogel and its bioapplication in tumor therapy and bone regeneration. Reprinted with permission from ref. ¹³⁶ © 2019, Wiley-VCH

bisphosphonate was the first molecule to be identified as being able to target bone. Multifunctional melanin-like nanoparticles based on alendronate-anchored polydopamine nanoparticle hybrid Fe were reported for the bone-targeted photothermal and chemotherapy of malignant bone tumors.¹⁶⁵ Alendronate possesses a high affinity for nanohydroxyapatite, resulting in targeted accumulation in the osteolytic bone site. The 7-ethyl-10-hydroxycamptothecin contained within the nanoparticles assisted with the cotherapy for efficient regression of the bone tumor. Additionally, carbon dots (CDs) synthesized from alendronate have strong binding activity for calcium-deficient hydroxyapatite.¹⁶⁶ Alendronate-based CDs (Alen-CDs) showed enhanced bone targeting in the bone structures of zebrafish and rat femurs compared to nitrogen-doped CDs using ethylenediamine (Alen-EDA-CDs). These results were attributed to the bisphosphonate group on the surface of the CDs even after carbonization. Recently, gold nanorods encapsulated in mesoporous silica nanoparticles conjugated with zoledronic acid (Au@MSNs-ZOL) were prepared for bone-targeted assisted inhibition of the proliferation of osteoclast-like cells and the promotion of osteogenic differentiation (Fig. 5).¹⁶⁷ The targeted photothermal therapy was enhanced to cure breast tumor bone metastasis in the hindlimbs of nude mice. This Au@MSNs-ZOL nanosystem was capable of curing the tumor, relieving pain, and inhibiting bone reabsorption for breast cancer bone metastasis treatment.

Although bisphosphonates are widely used as clinical drugs in metastatic bone tumor treatment, they may cause adverse effects such as atypical femoral fractures and esophageal cancer after long-term use.¹⁶⁸ In a recent study by Cheng Yiyun's group,¹⁶⁹ phytic acid (PA)-capped platinum (Pt) nanoparticles were developed for bone-targeting therapy. PA is a natural compound that contains six phosphate groups, indicating its high bone-targeting capability. In addition, PA shows an inherent anticancer ability, which can be combined with the Pt nanoparticle photothermal therapy. An in situ bone tumor model was established by engrafting PC-9-Luc cells in the tibias of nude mice, which can be detected by imaging the luminescence of the tumor regions. After PA/Pt nanosystem treatment, PA led to an enhancement of the PA/Pt nanoparticles at the tumor site. Additionally, PA/Pt nanoparticle-associated cotherapy inhibited tumor invasion.

DISCUSSION AND PERSPECTIVE

From the review on the recent development of bifunctional biomaterials in bone tumor therapy, a promising new strategy was introduced. According to the method of administration, bifunctional biomaterials can be divided into those delivered by local or systemic administration. Locally administered biomaterials mainly include 3D-printed scaffolds, nano/microparticle-containing scaffolds, and hydrogels. The representative systemically administered biomaterial is bone-targeting nanoparticles. A similarity and difference exist between these two types of biomaterials. The similarity is that a localized photothermal effect is used to kill tumor cells to prevent recurrence early on. The difference lies in the mechanism of bone repair. Locally administered scaffolds can be designed to match the bone defect area, and active molecules can be carried into the scaffold to stimulate bone regeneration. Systemically administered nanoparticles target bone tissues to inhibit bone reabsorption. The former is an example of positive regulation of bone regeneration, and the latter represents negative regulation of bone reabsorption. Although their mechanisms of bone repair are different, their outcomes in bone tumor therapy are similar.

For further development, there are three possible directions for bifunctional biomaterials for tumor therapy, and bone repair

may arise. First, NIR-II window-responsive biomaterials for photothermal therapy have been developed for deep tumor treatment, as mild photothermal effects can effectively protect bone tissue. For example, a recent study reported the use of bifunctional CDs combined with WS₂ to cure osteosarcoma under laser irradiation at 1064 nm.¹⁷⁰ Even when covered with a chicken breast with a thickness of 10 mm, the deep bone tumor was able to be killed. Moreover, mild photothermal effects (~43 °C) reported in recent studies can not only greatly enhance the proliferation of MSCs but also promote osteogenesis.^{171–175} This is good news for bone tumor therapy. The mild photothermal effect was shown to stimulate and accelerate in vitro and in vivo osteogenesis.^{170,176} Second, future treatment strategies for bone tumor therapy may not be limited to photothermal therapy and chemotherapy combined with biomaterials, and other therapeutic strategies, such as radio-chemotherapy and gas therapy, may also be potential methods to treat malignant bone tumors.^{171,172} Third, scaffolds developed in the future may need to be multifunctional, considering infection along with tumor therapy and bone regeneration.^{177,178} During tumor surgery, bleeding and soft tissue defects need to be considered. As shown in Fig. 6, a nanohydroxyapatite/graphene oxide/chitosan (nHA/GO/CS) scaffold was designed to inhibit osteosarcoma growth with mild photothermal therapy and mildly high temperature (~42 °C) to promote the osteogenesis of hBMSCs.¹⁷⁹ Furthermore, this scaffold showed a good hemostatic effect that can improve soft tissue regeneration.

New strategies based on bifunctional biomaterials for bone tumor therapy have the potential to extend to the treatment of other types of tumors (such as melanoma, oral tumors, and breast tumors), as well as damaged neighboring normal tissues. Melanoma treatment requires the complicated removal of tumor tissue and cutaneous defect repair.^{173–175} Oral tumors simultaneously destroy the facial bone. In clinical treatment, doctors remove oral tumor tissues along with the surrounding jawbone then collect the patient's fibula and use it to replace the jawbone with vascular anastomosis. Breast tumor treatment involves curing the residual tumor after surgical resection and breast defect regeneration.¹⁸⁰ Thus, the treatment of breast tumors relates to tumor therapy and adipose tissue engineering. In the latest study by Huang's group, a bifunctional 3D-printed dopamine-modified alginate scaffold was used to kill breast tumors and fill the defective breast area.²³ Researchers found a favorable photothermal effect from this scaffold to illuminate breast tumors. Additionally, the modulus of the scaffold was similar to that of normal breast tissue, and the scaffold enhanced the proliferation of breast epithelial cells. This method design can be used as a potential strategy for the prevention of breast tumor recurrence after surgery and adipose tissue repair. Future research should be focused on tumor therapy and tissue engineering for other complex diseases.

Although the use of bifunctional biomaterials for bone tumor therapy is developing rapidly, there is still a long way to go. The bifunctional biomaterial strategy further shows great potential for the treatment of complex diseases combined with tumor and tissue defects. Great confidence in researchers and clinicians will push this new strategy forward to solve clinical problems.

CONCLUSION

This review highlights the recent development of bifunctional biomaterials for bone tumor therapy. A new strategy based on bifunctional biomaterials can inhibit tumor growth in the early treatment period and enhance bone repair in the late treatment period. Photothermal therapy for tumor treatment has a short duration, but bone regeneration takes a long time.

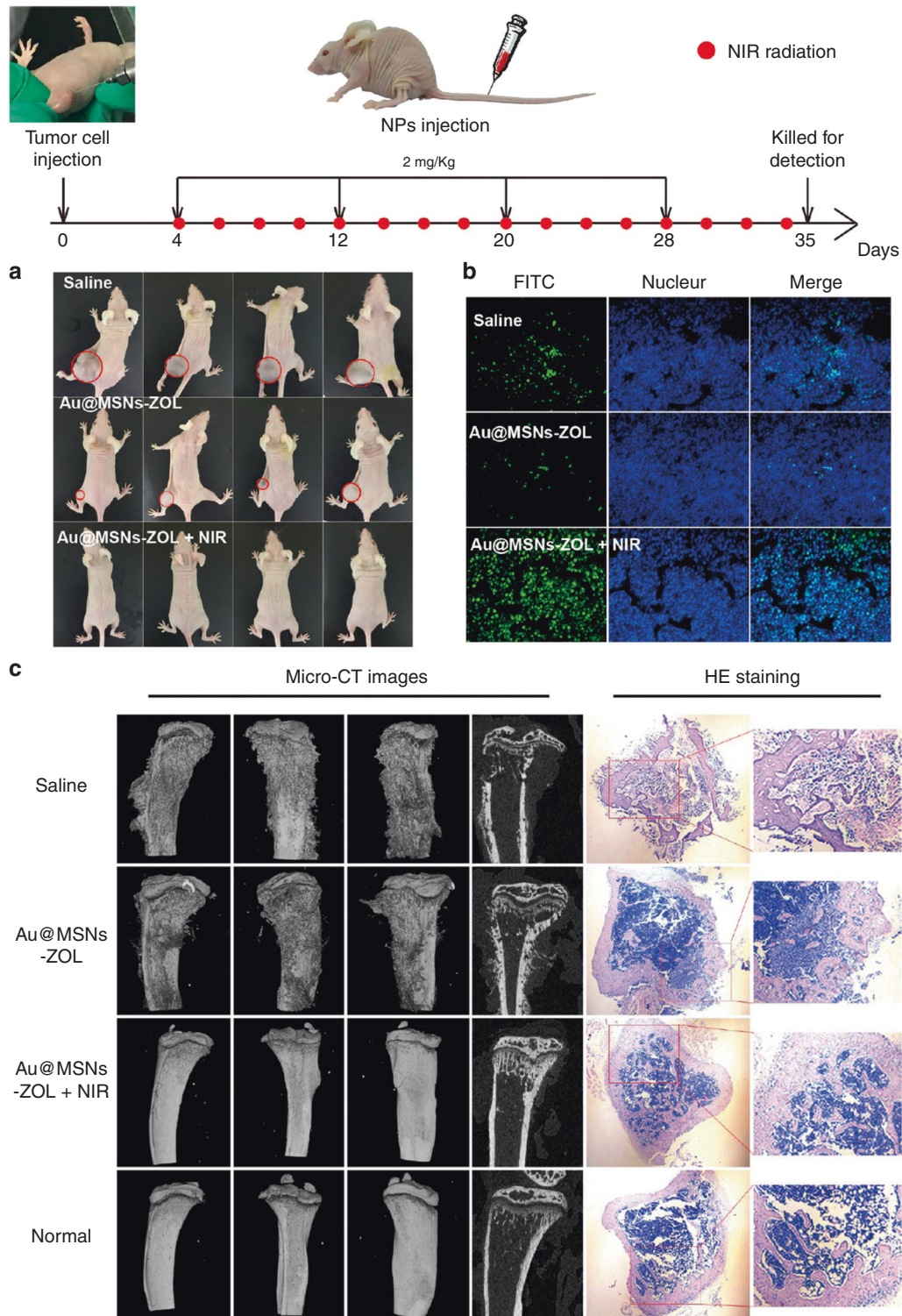


Fig. 5 Bone-targeted nanoplatform combining zoledronate and photothermal therapy to treat breast cancer bone metastasis. Top: Timeline of the treatment schedule. A breast cancer bone metastasis mouse model was established by direct injection of MDA-MB-231 cells into the left hindlimbs of nude mice. Nanoparticles and NIR irradiation were administered as indicated. **a** Images of tumor-bearing nude mice recorded at the end of treatment (day 35). **b** TUNEL fluorescence detected in the tumor slices. **c** CT images of the tibias from different angles and micrographs of H&E-stained tibias (right). Reprinted with permission from ref. ¹⁶⁷ © 2019, ACS Publications

With the benefits of locally administered (3D-printed scaffolds, nano/microparticle-containing scaffolds, and hydrogels) and systemically administered (bone-targeting nanoparticles) bifunctional biomaterials, the survival rate of bone tumor

patients has great potential to increase. Bifunctional biomaterial treatment may provide new hope for future clinical bone tumor therapy while improving patient quality of life and decreasing mortality.

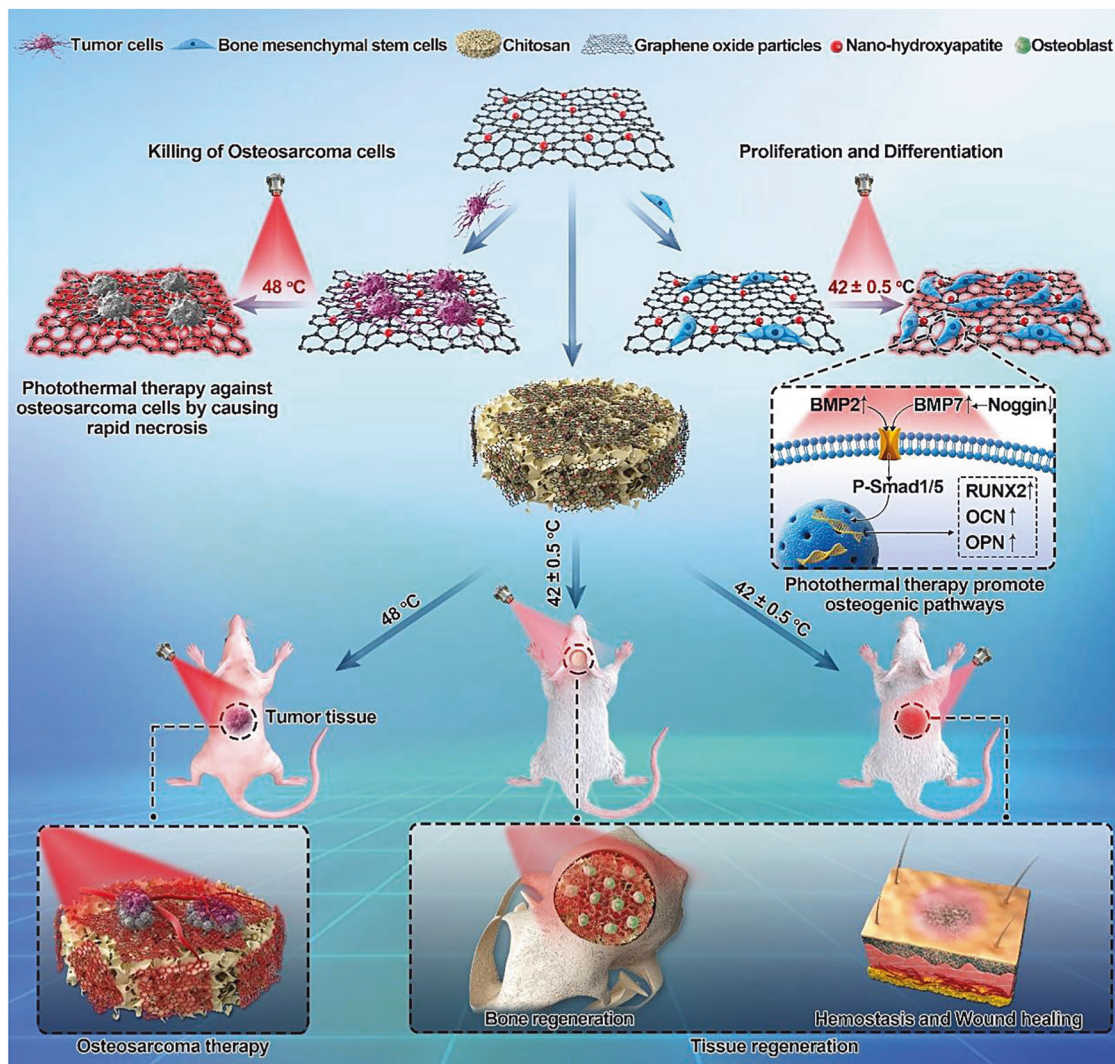


Fig. 6 Schematic illustration of the nanohydroxyapatite/graphene oxide/chitosan (nHA/GO/CS) scaffold for osteosarcoma treatment under photothermal therapy and the promotion of tissue regeneration. Reprinted with permission from ref. ¹⁷⁹ © 2020, RSC Publishing

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ADDITIONAL INFORMATION

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